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EDITORIAL

The role of stromal BMP/CXCL12 signaling axis in serrated polyp development

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Colorectal cancer (CRC) is the third most common type of cancer and the second most common cause of cancer-related death worldwide [1]. To improve the prognosis of CRC, it is important to understand the molecular mechanisms underlying the initiation of colorectal carcinogenesis. CRCs mainly arise from adenoma through "conventional pathway" [2]. Approximately thirty percentage of CRCs arise from serrated lesions including hyperplastic polyps (HPs), sessile serrated lesions (SSLs), and traditional serrated adenomas (TSAs) through "serrated pathway" [1, 3, 4]. Three–five percentage of CRCs were associated with hereditary disorders with germline mutations such as the hereditary nonpolyposis colorectal cancer, best known as Lynch syndrome, the familial adenomatous polyposis, and juvenile polyposis syndrome (JPS), serrated polyposis syndrome with the lowest incidence (< 0.1%) [5–7].

JPS is a rare hereditary disorder which forms numerous hamartomatous polyps throughout gastrointestinal tract, which increase a lifetime risk of developing gastrointestinal cancer. Fifty–sixty percentage of JPS patients harbor germline mutations in *SMAD4* and *BMPR1A* [8, 9]. The mutations in *SMAD4* and *BMPR1A* found in JPS suggest that the BMP pathway plays a pivotal role for polyp development, however, it was unclear how these mutations contribute to polyp formation.

BMP is one of the members of the TGF-β superfamily. The activated BMP receptor phosphorylates SMAD1/5/8, which binds SMAD4 and translocates to the nucleus to regulate gene transcription [10]. Previous studies showed that abrogation of BMP signaling in the intestinal epithelium alone is not sufficient for polyp formation [11] and that BMP signaling loss in the stroma is sufficient to initiate polyp development [12]. However, it remains to be elucidated precisely which stromal cell type could contribute to polyp formation, and the molecular mechanism behind the polyp formation upon loss of BMP signaling was unknown.

Recently, Ouahoud et al. clarified the role of BMP signaling in stromal cells (i.e., fibroblasts, myofibroblasts, and endothelial cells) in the intestines using each cell type-specific Cre mice (*Colla2*, *Sm22*, and *VeCad*-expressing cells, respectively) [13]. Murine endothelial cells-specific knockout of *BMPR1A* did not affect intestinal homeostasis, whereas fibroblasts-specific or myofibroblasts-specific knockout of *BMPR1A* resulted in polyp development in the intestines. Surprisingly, these polyps did not resemble human hamartomatous polyp, but instead, resembled human SSL. Human SSL is associated with activation of the MAPK/ERK pathway and *BRAF* mutations [3, 4]. The immunostaining of phospho-Erk showed that the activity of MAPK/ERK pathway was increased in mouse serrated polyps. This study for the first time revealed that loss of BMP signaling in fibroblasts or myofibroblasts, but not endothelial cells, leads to serrated polyp development.

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To investigate whether the *BMPR1A* deficiency (BMPR1AD) in fibroblasts increases the proliferation of intestinal epithelium in vitro, they co-cultured BMPR1AD fibroblasts with normal mouse intestinal organoids and found that BMPR1AD fibroblasts significantly promotes intestinal organoid growth compared to control fibroblasts.

Additionally, the authors showed that CXCL12, a homeostatic chemokine, was expressed by intestinal fibroblasts and that CXCL12 expression in intestinal fibroblasts was upregulated by fibroblasts-specific *BMPR1A* deletion. They found that treatment of a selective BMPR1A inhibitor or a BMP antagonist increased CXCL12 expression in the human colon fibroblasts. These data suggested that BMP signaling regulates CXCL12 expression in fibroblasts. Moreover, administration of recombinant CXCL12 in murine intestinal organoids resulted in hyperproliferation of intestinal epithelial cells. Notably, restoring BMP activity by a ligand-independent activator of the BMP pathway or inhibition of CXCL12 by a CXCL12 neutralizing ligand dramatically reduced the number of polyps compared to the mice treated with vehicle in vivo. Therefore, this study for the first time identified the role of stromal BMP–CXCL12 signaling axis in serrated polyp development.

CRCs were subdivided into four Consensus Molecular Subtype (CMS) with distinguishing features [14]. CMS4 (mesenchymal subtype) had overexpression of stromal invasion, mesenchymal activation, and complement pathways gene set. CMS4 tumors have worse overall survival and worse relapse-free survival [14]. Both the BMP antagonists; *NOGGIN* and *GREMLIN1*, and *CXCL12* were most highly expressed in CMS4 CRCs among all CMSs in this study. CXCL12 secreted by cancer-associated fibroblasts and the chemokine receptor CXCR4 found on T cells appear to drive immunosuppression in the tumor microenvironment [15]. Thus, future studies may clarify therapeutic potential of targeting immune milieu in CMS4 CRCs associated with SSL [16].

In summary, Ouahoud et al. demonstrated that loss of *BMPR1A*, specifically in fibroblasts or myofibroblasts but not endothelial cells, results in CXCL12-driven hyperproliferation of intestinal epithelial cells and serrated polyp development. Further investigation is required to determine whether the stromal BMP–CXCL12 signaling axis also contributes to serrated polyp development in humans and hamartomatous polyp development in JPS.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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